

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
12 February 2004 (12.02.2004)

PCT

(10) International Publication Number
WO 2004/012730 A1

(51) International Patent Classification⁷: **A61K 31/38**, 9/70

(21) International Application Number:
PCT/EP2003/008320

(22) International Filing Date: 28 July 2003 (28.07.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02016860.5 30 July 2002 (30.07.2002) EP

(71) Applicant: **SCHWARZ PHARMA AG** [DE/DE]; Alfred-Nobel-Strasse 10, 40789 Monheim (DE).

(72) Inventors: **HANNAY, Mike**; Gudenauer Busch 7, 53343 Wachtberg-Villiprott (DE). **SCHACHT, Dietrich, Wilhelm**; Dürener Strasse 396, 50935 Köln (DE). **WOLFF, Hans-Michael**; Richard-Wagner-Strasse 2, 40789 Monheim (DE).

(74) Agents: **HOFFMANN EITLE** et al.; Arabellastrasse 4, 81925 München (DE).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **IMPROVED TRANSDERMAL DELIVERY SYSTEM FOR THE ADMINISTRATION OF ROTIGOTINE**

(57) Abstract: An improved Transdermal Delivery System (TDS) comprising a backing layer inert to the components of the matrix, a self-adhesive matrix containing rotigotine and a protective foil or sheet to be removed prior to use, characterized in that the self-adhesive matrix consists of a solid or semi-solid semi-permeable polymer (1) wherein rotigotine in its free base form has been incorporated, (2) which is saturated with rotigotine and contains said rotigotine as a multitude of microreservoirs within the matrix, (3) which is highly permeable for the free base of rotigotine, (4) which is impermeable for the protonated form of rotigotine, (5) wherein the maximum diameter of the microreservoirs is less than the thickness of the matrix. is provided. Said TDS provides for enhanced flux of rotigotine across the TDS/skin interface.

WO 2004/012730 A1

**Improved Transdermal Delivery System for the Administration
of Rotigotine**

5 FIELD OF INVENTION

The present invention relates to an improved transdermal delivery system for rotigotine. Moreover, the invention relates to a method of treatment using the transdermal
10 delivery system.

TECHNICAL BACKGROUND

To date, various transdermal delivery systems (TDS) for the
15 administration of rotigotine have been described.
WO 94/07568 discloses a TDS containing rotigotine hydrochloride as active substance in a two-phase matrix, which is essentially formed by a hydrophobic polymer material as the continuous phase and a disperse hydrophilic phase
20 contained therein and mainly containing the drug and hydrated silica. The silica is said to enhance the maximum possible loading of the TDS with the hydrophilic salt. Moreover, the formulation of WO94/07568 usually contains additional hydrophobic solvents, permeation promoting substances
25 dispersing agents and, in particular, an emulsifier which is required to emulsify the aqueous solution of the active component in the lipophilic polymer phase. A TDS prepared by using such a system has been tested in healthy subjects and Parkinson's patients. However, no satisfactory drug plasma
30 levels were achieved.

Various further TDS have been described in WO99/49852. The TDS used in this patent application comprises a backing layer, inert with respect to the constituents of the matrix,
35 a self-adhesive matrix layer containing an effective quantity of rotigotine hydrochloride or rotigotine, which contains a substantial amount of rotigotine hydrochloride (>5 % w/w), and a protective film, which is to be removed before use.

The matrix system is composed of a non-aqueous polymer adhesive system, based on acrylate or silicone, with a solubility of rotigotine of at least 5% w/w. Said matrix has been described as being essentially free of inorganic
5 silicate particles. However, even the TDS described in WO99/49852 leave something to be desired as regards the obtainable flux rates of drug across human skin.

In the TDS according to WO94/07568 and many related
10 applications, passive diffusion membranes were used.

However, as the skin is to be seen as a very efficient barrier for most drug candidates, such type of membrane controlled systems are more or less limited in practice to
15 transdermal delivery of active substances that reveal a very high skin permeability. Additionally, special requirements on drug release kinetics have to be met like contact delivery over several days.

20 An object of the present invention is to control (i.e. to canalise/manoeuvre) the transport of rotigotine towards and across the skin from a drug reservoir, thereby enhancing the flux of rotigotine across the TDS/skin interface.

25 A further object and aspect of the present invention is to provide a suitable composition and manufacturing methods of polymer matrices in TDS which lead to an enhanced delivery of rotigotine to and across the skin by

- 30 (i) preventing back diffusion of the drug portion which is ionized in the skin according to its pKa value - from the skin tissue into the TDS,
(ii) offering continuous delivery of the active compound across the stratum corneum not only via the common
35 more lipophilic route (e.g. intercellular) but also through hydrophilic pores (e.g. eccrine sweat glands).

SUMMARY OF THE INVENTION

These objects are solved by providing a TDS comprising a
5 backing layer inert to the components of the matrix, a self-
adhesive matrix containing rotigotine and a protective foil
or sheet to be removed prior to use,

characterized in that

10 the self-adhesive matrix consists of a solid or semi-solid
semi-permeable polymer

- 15 (1) wherein rotigotine in its free base form has been
incorporated,
- (2) which is saturated with rotigotine and contains
said rotigotine as a multitude of microreservoirs
within the matrix,
- 20 (3) which is highly permeable for the free base of
rotigotine,
- (4) which is impermeable for the protonated form of
rotigotine,
- 25 (5) wherein the maximum diameter of the
microreservoirs is less than the thickness of the
matrix.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows the effect of the protonation of rotigotine in
30 the semi-permeable matrix on the drug absorption.

Fig. 2 shows the impact of the size distribution of the
microreservoirs in the semi-permeable matrix on the drug
absorption.

35 Fig. 3 shows the effect of reducing the amount of the
protonated form of rotigotine in the semi-permeable matrix

and reducing the size of the microreservoirs on the drug absorption.

Fig. 4 shows a microscope image of a conventional TDS.

5

Fig. 5 shows a microscope image of the TDS according to the invention.

Fig. 6 shows the effect of reducing the amount of the protonated form of rotigotine in the semi-permeable matrix and reducing the size of the microreservoirs on the in vitro skin permeation of the drug.

10

Fig. 7 shows a comparison of the in vitro skin permeation of rotigotine for the TDS of the invention and an acrylate-based TDS.

15

DESCRIPTION OF THE INVENTION

The present invention provides a TDS providing a high steady state flux rate of rotigotine over the TDS/skin interface.

20

Surprisingly, it was found that drug release properties of a TDS having a silicone-type adhesive matrix containing rotigotine can be significantly enhanced by

25

(1) minimizing the amount of rotigotine which is present in the protonated form (salt form);

(2) incorporating rotigotine in a multitude of microreservoirs within the self-adhesive matrix consisting of a solid or semi-solid semi-permeable polymer.

30

The impact of above described measures on drug release characteristics of rotigotine in vivo is illustrated in Figs. 1, 2 and 3. The relative drug absorption in vivo was

35

highest for the sample according to the invention; increase of the size of the microreservoirs and/or the amount of drug salt residues in the TDS led to slower initial drug release.

- 5 Based on the above findings, the present invention was accomplished.

When using the TDS, according to the present invention, a high transfer of rotigotine from the silicone matrix into the
10 outermost skin layer can be achieved. Consequently, plasma values of rotigotine are sufficient to allow for a reasonable expectation that an efficient treatment with fewer side effects can be provided.

- 15 The drug contained in the TDS according to the invention is 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol (INN: rotigotine). Rotigotine is a dopamine D2 receptor antagonist, which is useful for example in the treatment of Parkinson's disease.

20 It should be understood that the term "treatment" in the context of this application is meant to designate a treatment or an alleviation of the symptoms. The treatment may be of a therapeutic or prophylactic nature.

25 It will be understood by a person skilled in the art that rotigotine exists in various isomeric forms. It has to be understood that any single isomer or a mixture of different isomers may be used in the TDS according to the invention.

- 30 Hence, the S- or R-enantiomer or the racemate or any other enantiomer mixture of rotigotine may be used.

At least a part of rotigotine is contained in a multitude of microreservoirs distributed within the self-adhesive matrix
35 of the TDS according to the invention. This does not exclude and will normally even imply that a certain fraction of rotigotine is dissolved in the solid or semi-solid semi-

permeable polymer of the matrix at its saturation concentration.

Within this specification "microreservoirs" are meant to be
5 understood as particulate, spatially and functionally
separate compartments consisting of pure drug or a mixture of
drug and crystallization inhibitor, which are dispersed in
the self-adhesive (polymer) matrix. Preferably the self-
adhesive matrix contains 10^3 to 10^9 microreservoirs per cm^2
10 of its surface, particularly preferred are 10^6 to 10^9
microreservoirs per cm^2 .

Rotigotine is incorporated in the self-adhesive matrix in its
free base form. This does not totally exclude the presence
15 of some residual salt form of rotigotine in the final TDS.
However, the salt form of rotigotine should be contained in
the self-adhesive matrix of the final TDS in an amount of
preferably less than 5 %, more preferably less than 2 %,
particularly less than 1 % (w/w).

20

If rotigotine is present in the self-adhesive matrix in its
protonated (salt) form, it will not be released by the self-
adhesive matrix. Thus, the amount of the salt form of
rotigotine can be determined by performing a drug dissolution
25 test according to the Paddle over Disk method as described in
the United States Pharmacopeia (United States
Pharmacopeia/New Formulary (USP25/NF20), Chapter 724 "Drug
Release", United States Pharmacopeial Convention, Inc.,
Rockville, MD 20852, USA (2002)), using the following
30 conditions: dissolution medium: 900 ml phosphate buffer
pH 4.5; temperature adjusted to $32 \pm 0.5^\circ\text{C}$; paddle rotation
speed: 50 rpm; sampling times: 0.5, 1, 2 and 3 h,
respectively. The increase in the eluted rotigotine
concentration can be used to calculate the amount of
35 unprotonated rotigotine in the matrix.

The amount of the salt form of rotigotine may be reduced e.g. by reducing the water content of the mass containing the drug and organic solvent(s). In a particularly preferred embodiment of the invention the water content is reduced during manufacture to preferably less than 0.4 % (w/w), more preferably less than 0.1 %, of the mass.

A further step, which may be taken for reducing the amount of the salt form of rotigotine, is isolating the free base form of rotigotine in solid form prior to the preparation of the TDS. If the free base of rotigotine is produced in situ during the manufacture of the TDS by neutralizing an acid addition salt, a certain residue of the ionized drug form will remain in the polymer matrix (usually > 5 % (w/w) and up to approximately 10 %). Therefore, such in situ preparation of the free base form will generally not be suitable for practising the present invention.

The maximum diameter of the microreservoirs is less than the thickness of the matrix, preferably up to 70 % of the thickness of the matrix, particularly preferably 5 to 60 % of the thickness of the matrix. For an exemplary thickness of the matrix of 50 μm this corresponds to a maximum diameter of the microreservoirs in the range of preferably up to 35 μm .

The term "maximum diameter" is meant to be understood as the diameter of the microreservoirs in one dimension (x-, y-, or z-dimension), which is the largest. It is clear to the skilled person that in case of spherical diameters the maximum diameter corresponds to the microreservoir's diameter. However, in the case of microreservoirs, which are not shaped in the form of spheres - i.e. of different geometric forms -, the x-, y- and z-dimensions may vary greatly.

As the maximum diameter of the microreservoirs in the direction of the cross-section of the matrix, i.e. between the release surface and the backing layer, is less than the

thickness of the matrix, direct contact between the skin and the basic microreservoirs containing rotigotine is avoided, if not at all prevented. Owing to the slightly acidic pH of the skin, direct contact between the skin and the
5 microreservoirs in the matrix leads to protonation of rotigotine, thereby deteriorating the semi-permeability of the matrix.

In a particularly preferred embodiment of the invention, the
10 mean diameter of the microreservoirs containing rotigotine distributed in the matrix is in the range of 1 to 40 %, even more preferably 1 to 20 %, of the thickness of the drug-loaded self-adhesive matrix. For an exemplary thickness of the matrix of 50 μm this corresponds to a mean diameter of
15 the microreservoirs in the range of preferably 0.5 to 20 μm . The term "mean diameter" is defined as the mean value of the x,y,z-average diameters of all microreservoirs. The target particle size can be adjusted by the solids content and viscosity of the drug-containing coating mass.

20 The maximum and mean diameters of the microreservoirs as well as the number of microreservoirs per surface area of the self-adhesive matrix can be determined as follows: The release liner is removed from the TDS, and the free adhesive
25 surface is examined with a light microscope (Leica microscope type DM/RBE equipped with a camera type Basler A 113C). The measurement is performed by incidental polarized light analysis using a microscope at 200x magnification. A picture analysis is performed using the software Nikon Lucia_Di,
30 Version 4.21, resulting in mean and maximum diameters for each sample.

The TDS of the present invention is of the "matrix" type. In such matrix type TDS the drug is dispersed in a polymer
35 layer. The TDS of the matrix type in their simplest version comprise a one-phase (monolayer) matrix. They consist of a backing layer, a self-adhesive matrix containing the active

agent and a protective foil or sheet, which is removed before use.

Versions that are more complicated comprise multi-layer matrixes, wherein the drug may be contained in one or more non-adhesive polymer layers. The TDS of the present invention is preferably a one-phase (mono layer) matrix system.

10 The solid or semi-solid semi-permeable polymer of the self-adhesive matrix has to satisfy the following requirements:

1. Sufficient solubility and permeability for the free base form of rotigotine.

15

2. Impermeability for the protonated form of rotigotine.

In a particular preferred embodiment of the invention the self-adhesive matrix is free of particles that can absorb salts of rotigotine on the TDS/skin interface. Examples of particles that can absorb salts of rotigotine on the TDS/Skin interface include silica. Such particles that can adsorb salts of rotigotine may represent diffusion barriers for the free base form of the drug and may result in the formation of channels inducing some permeability of the self-adhesive matrix for the protonated form of rotigotine. Such embodiments are therefore disadvantageous for practising the invention.

30 The self-adhesive matrix of the TDS of the present invention consists of a solid or semi-solid semi-permeable polymer. Usually this polymer will be a pressure sensitive adhesive (PSA) or a mixture of such adhesives. The pressure sensitive adhesive(s) form a matrix in which the active ingredient and the other components of the TDS are incorporated.

35

The adhesive used in the present invention should preferably be pharmaceutically acceptable in a sense that it is biocompatible, non-sensitising and non-irritating to the skin. Particularly advantageous adhesives for use in the present invention should further meet the following requirements:

1. Retained adhesive and co-adhesive properties in the presence of moisture or perspiration, under normal temperature variations,
2. Good compatibility with rotigotine, as well as with the further excipients used in the formulation.

Although different types of pressure sensitive adhesive may be used in the present invention, it is preferred to use lipophilic adhesives having both a low drug and low water absorption capacity. Particular preferably, the adhesives have solubility parameters which are lower than those of rotigotine. Such preferred pressure sensitive adhesives for use in the TDS of the present invention are silicone type pressure sensitive adhesives. Especially preferred pressure sensitive adhesives for use in the TDS of the invention are of the type forming a soluble polycondensed polydimethylsiloxane (PDMS) / resin network, wherein the hydroxy groups are capped with e.g. trimethylsilyl (TMS) groups. Preferred adhesives of this kind are the BIO-PSA silicone pressure sensitive adhesives manufactured by Dow Corning, particularly the Q7-4201 and Q7-4301 qualities. However, other silicone adhesives may also be used.

In a further and especially preferred aspect, two or more silicone adhesives are used as the main adhesive components. It can be advantageous if such a mixture of silicone adhesives comprises a blend of high tack silicone pressure sensitive adhesive comprising polysiloxane with a resin and a

medium tack silicone type pressure sensitive adhesive comprising polysiloxane with a resin.

Tack has been defined as the property that enables an adhesive to form a bond with the surface of another material upon brief contact under light pressure (see e.g. "Pressure Sensitive Tack of Adhesives Using an Inverted Probe Machine", ASTM D2979-71 (1982); H.F. Hammond in D. Satas "Handbook of Pressure Sensitive Adhesive Technology" (1989), 2nd ed., Chapter 4, Van Nostrand Reinhold, New York, page 38).

Medium tack of a silicon pressure sensitive adhesive indicates that the immediate bond to the surface of another material is weaker compared to high tack silicon adhesive. The mean resin/polymer ratio is approx. 60/40 for medium tack adhesives, whereas it is approx. 55/45 for high tack adhesives. It is known to the skilled person that both tape and rheological properties are significantly influenced by the resin/polymer ratio (K.L. Ulman and R.P. Sweet "The Correlation of Tape Properties and Rheology" (1998), Information Brochure, Dow Corning Corp., USA).

Such a blend comprising a high and a medium tack silicone type pressure sensitive adhesive comprising polysiloxane with a resin is advantageous in that it provides for the optimum balance between good adhesion and little cold flux. Excessive cold flux may result in a too soft patch which easily adheres to the package or to patient's garments. Moreover, such a mixture seems to be particularly useful for obtaining higher plasma levels. A mixture of the aforementioned Q7-4201 (medium tack) and Q7-4301 (high tack) proved to be especially useful as a matrix for the TDS according to the present invention.

In a further preferred embodiment, the TDS further includes a crystallization inhibitor. Several surfactants or amphiphilic substances may be used as crystallization

inhibitors. They should be pharmaceutically acceptable and approved for use in medicaments. A particularly preferred example of such a crystallization inhibitor is soluble polyvinylpyrrolidone, which is commercially available, e.g. under the trademark Kollidon[®] (Bayer AG). Other suitable crystallization inhibitors include copolymers of polyvinylpyrrolidone and vinyl acetate, polyethyleneglycol, polypropyleneglycol, glycerol and fatty acid esters of glycerol or copolymers of ethylene and vinyl acetate.

The device of the present invention further comprises a backing layer, which is inert to the components of the matrix. This backing layer is a film being impermeable to the active compounds. Such a film may consist of polyester, polyamide, polyethylene, polypropylene, polyurethane, polyvinyl chloride or a combination of the aforementioned materials. These films may or may not be coated with an aluminium film or with aluminium vapour. The thickness of the backing layer may be between 10 and 100 μm , preferably between 15 and 40 μm .

The TDS of the present invention further comprises a protective foil or sheet, which will be removed immediately prior to use, i.e. immediately before the TDS will be brought into contact with the skin. The protective foil or sheet may consist of polyester, polyethylene or polypropylene which may or may not be coated with aluminium film or aluminium vapour or fluoropolymers. Typically the thickness of such a protective foil or sheet ranges from between 50 and 150 μm . So as to facilitate removal of the protective foil or sheet when wishing to apply the TDS, the protective foil or sheet may comprise separate protective foils or sheets having overlapping edges, similar to the kind used with the majority of conventional plasters.

In a preferred embodiment of the present invention, the TDS has a basal surface area of 5 to 50 cm^2 , particularly of 10

to 30 cm². It goes without saying that a device having a surface area of, say, 20 cm² is pharmacologically equivalent to and may be exchanged by two 10 cm² devices or four 5 cm² devices having the same drug content per cm². Thus, the surface areas as indicated herein should be understood to refer to the total surface of all devices simultaneously administered to a patient.

Providing and applying one or several TDS according to the invention has the pharmacological advantage over oral therapy that the attending physician can titrate the optimum dose for the individual patient relatively quickly and accurately, e.g. by simply increasing the number or size of devices given to the patient. Thus, the optimum individual dosage can often be determined after a time period of only about 3 weeks with low side effects.

A preferred content of rotigotine in the TDS according to the invention is in the range of 0.1 to 2.0 mg/cm². Still more preferred are 0.20 to 1.0 mg/cm². If a 7 day patch is desired, higher drug contents will generally be required.

The device used in the present invention is preferably a patch having a continuous adhesive matrix in at least its center portion containing the drug. However, transdermal equivalents to such patches are likewise comprised by the present invention, e.g. an embodiment where the drug is in an inert but non-adhesive matrix in the center portion of the device and is surrounded by an adhesive portion along the edges.

The TDS according to the present invention is prepared by a manufacturing process, which comprises preparing a rotigotine loaded adhesive, coating, drying or cooling and lamination to get the bulk product, converting the laminate into patch units via cutting, and packaging.

The invention and the best mode for carrying it out will be explained in more detail in the following non-limiting examples.

5 INVENTION EXAMPLE 1 (very low salt content, small microreservoirs)

252.6 g Rotigotine free base are dissolved in 587.8 g ethanol
100 % w/w and mixed with 222.2 g ethanolic solution
10 containing 25 % w/w polyvinylpyrrolidone (Kollidon F 90),
0.11 % w/w aqueous sodium bisulfite solution (10 % w/w), 0.25
% ascorbyl palmitate and 0.62 % DL- α -tocopherol. To the
homogenous mixture 1692.8 g BIO-PSA Q7 4301 (73 % w/w),
1691.6 g BIO-PSA Q7 4201 (73 % w/w) and 416.3 g petrol ether
15 are added and all components are stirred for at least 1 hour
to get a homogenous dispersion.

For manufacture of the patch matrix, the dispersion is coated
onto a suitable release liner (for example Scotchpak 1022)
20 and the solvents are continuously removed in a drying oven at
temperatures up to 80°C to get a drug-containing adhesive
matrix of 50 g/m² coating weight. The dried matrix film is
laminated with a polyester-type backing foil which is
siliconized on the inner side and aluminium vapor coated on
25 the opposite side.

The individual patches are punched out of the complete
laminate and are sealed into pouches under a nitrogen flow.

30 The rotigotine contained in the matrix was quantitatively
released after 3 hours in the drug dissolution test according
to the Paddle over Disk method as described in the USP using
the conditions as described above. This result indicates
that the obtained TDS was completely free of rotigotine
35 hydrochloride.

The mean size of the microreservoirs in the TDS was approx. 10 μm with typical sizes in the range of 5 to 35 μm . A microscope image of the obtained TDS is shown in Fig. 5.

5 COMPARATIVE EXAMPLE 1 (high salt content, small microreservoirs)

2400 g Rotigotine hydrochloride were added to a solution of 272.8 g NaOH in 3488 g ethanol (96 %). The resulting mixture
10 was stirred for approximately 10 minutes. Then 379.2 g of sodium phosphate buffer solution (27.6 g $\text{Na}_2\text{HPO}_4 \times 2\text{H}_2\text{O}$) and 53.2 g $\text{NaH}_2\text{PO}_4 \times 2\text{H}_2\text{O}$ in 298.5 g water) was added. Insoluble or precipitated solids were separated from the mixture by filtration. The filter was rinsed with 964 g ethanol (96 %)
15 to obtain a particle-free ethanolic solution of rotigotine essentially in the form of the free base.

The rotigotine solution (6150 g) in ethanol (30 % w/w) was mixed with 407 g ethanol (96 %). The resulting solution was
20 mixed with 1738.8 g of an ethanolic solution containing 25 wt.% polyvinylpyrrolidone (Kollidon[®] 90F), 0.11 wt.% aqueous sodium bisulfite solution (10 wt.%), 0.25 wt. % ascorbyl palmitate, and 0.62 wt.% DL-alpha-tocopherol until homogeneity. To the mixture 13240 g of an amine resistant
25 high tack silicone adhesive (BIO-PSA[®] Q7-4301 mfd. by Dow Corning) (73 wt.% solution in heptane), 13420 g of an amine resistant medium tack silicone adhesive (BIO-PSA[®] Q7-4201 mfd. by Dow Corning) (72 wt.% solution in heptane), and 3073 g petrol ether were added, and all components were stirred
30 until a homogenous dispersion was obtained.

The dispersion was coated onto a suitable polyester release liner (SCOTCHPAK[®] 1022) with a suitable doctor knife and the solvents were continuously removed in a drying oven at
35 temperatures up to 80°C for about 30 minutes to obtain a drug containing adhesive matrix of 50 g/m² coating weight. The dried matrix film was laminated with a polyester-type backing

foil (SCOTCHPAK[®] 1109). The individual patches were punched out of the complete laminate in the desired sizes (e.g. 10 cm², 20 cm², 30 cm²) and sealed into pouches under the flow of nitrogen.

5

Only approx. 95 % of the rotigotine contained in the matrix were released after 3 hours in the drug dissolution test according to the Paddle over Disk method as described in the USP using the conditions as described above. Thus, the
10 obtained TDS contained approx. 5 % (w/w) of protonated rotigotine.

The mean size of the microreservoirs in the TDS was approx. 15 μ m with typical sizes in the range of 10 to 20 μ m.

15

COMPARATIVE EXAMPLE 2 (high salt content, large microreservoirs)

150 g Rotigotine hydrochloride were added to a solution of
20 17.05 g NaOH in 218 g ethanol (96%). The resulting mixture was stirred for approximately 10 minutes. Then 23.7 g of sodium phosphate buffer solution (8.35 g Na₂HPO₄x2H₂O and 16.07 g NaH₂PO₄x2H₂O in 90.3 g water) was added. Insoluble or precipitated solids were separated from the mixture by
25 filtration. The filter was rinsed with 60.4 g ethanol (96 %) to obtain a particle-free ethanolic solution of rotigotine essentially in the form of the free base.

The rotigotine solution (346.4 g) in ethanol (35 % w/w) was
30 mixed with 36.2 g ethanol (96%). The resulting solution was mixed with 109 g of an ethanolic solution containing 25 wt% polyvinylpyrrolidone (KOLLIDON[®] 90F), 0.077 wt% aqueous sodium bisulfite solution (10 wt%), 0.25 wt% ascorbyl palmitate, and 0.63 wt% DL-alpha-tocopherol until homogenous.
35 To the mixture, 817.2 g of an amine resistant high tack silicone adhesive (BIO-PSA[®] Q7-4301 mfd. by Dow Corning) (74 wt% solution in heptane), 851.8 g of an amine resistant

medium tack silicone adhesive (BIO-PSA® Q7-4201 mfd. by Dow Corning) (71 wt% solution in heptane), and 205.8 g petrol ether (heptane) were added, and all components were stirred until a homogenous dispersion was obtained.

5

The dispersion was coated onto a suitable polyester release liner (SCOTCHPAK® 1022) with a suitable doctor knife and the solvents were continuously removed in a drying oven at temperatures up to 80°C for about 30 min to obtain a drug-
10 containing adhesive matrix of 50 g/m² coating weight. The dried matrix film was laminated with a polyester-type backing foil (SCOTCHPAK® 1109). The individual patches were punched out of the complete laminate in the desired sizes (e.g. 10 cm², 20 cm², 30 cm²) and sealed into pouches under the
15 flow of nitrogen.

Owing to the large microreservoirs in the TDS' matrix, it was possible to dissolve the rotigotine salts by direct contact with the dissolution medium. Thus, it was not possible to
20 determine the amount of the protonated form of rotigotine. This indicates that the maximum diameter of the microreservoirs was larger than the thickness of the matrix.

The mean size of the microreservoirs in the TDS was approx.
25 50 µm with typical sizes in the range of 20 to 90 µm. A microscope image of the obtained TDS is shown in Fig. 4.

As rotigotine was released from rotigotine hydrochloride in a manner similar to Comparative Example 1, one may conclude
30 that the obtained TDS also contained 5 % (w/w) of rotigotine in its protonated form.

COMPARATIVE EXAMPLE 3 (Acrylate-type formulation)

35 A mixture of 50.0 g rotigotine hydrochloride and 28.6 g sodium trisilicate in 95 g methyl ethyl ketone was stirred at room temperature for 48 hours. Subsequently, 17.9 g oleic

alcohol, 128.6 g of an acrylic-type adhesive solution (51.4 % w/w in ethyl acetate; trade name: Durotak[®] 387-2287 from NATIONAL STARCH & CHEMICAL), 33.0 g of EUDRAGIT[®] E100 (from ROEHM PHARMA) (50 % w/w solution in ethyl acetate) and
5 45.0 g ethyl acetate were added, and the mass was homogenised mechanically.

The dispersion was coated onto a suitably siliconised process liner (Hostaphan[®] RN 100), and the solvents were evaporated
10 at 50°C over 30 minutes, thereby obtaining a matrix weight of 60 g/m². The dry film was laminated with a suitable polyester foil (Hostaphan[®] RN 15). Individual patches having a desired size of (e.g. 20 cm²) were punched out of the resulting laminate and sealed into pouches under the flow of nitrogen.

15

EXAMPLE 2

In vivo drug absorption test

In order to monitor the absorption of rotigotine by the human
20 skin the following experiment was carried out. The test was performed with the TDS obtained in Example 1 as well as in Comparative Examples 1 and 2.

The plasma concentration time profile at different test times
25 was determined in pharmacokinetic studies involving (A) 14 healthy male persons (TDS of Comparative Examples 2 and 3) or (B) 30 healthy male persons (TDS of Example 1 and Comparative Example 1), respectively. The studies were conducted following an open single-dose randomised (B) two-way or (A)
30 three-way cross-over design.

Individual concentrations of rotigotine were determined by means of liquid chromatography and mass spectroscopy. The lower limit of quantification (LOQ) was 10 pg/ml.

35

The drug absorption was calculated from the plasma concentration data according to the Wagner-Nelson method

(Malcom Rowland, Thomas N. Tozer (Eds.) "Estimation of Adsorption Kinetics from Plasma Concentration Data" in Clinical Pharmacokinetics, pp 480-483, Williams & Wilkins, 1995), 100 % = absorption rate after 48 hours; patch application time was 24 hours.

A comparison of the flux across human skin for the different TDS tested is shown in Fig. 1, 2 and 3.

In Fig. 1 the rotigotine absorption for the sample obtained in Example 1 containing no salt (O) is compared to the sample obtained in Comparative Example 1 containing approx. 5 % (w/w) of rotigotine hydrochloride (●). The comparison in Fig. 1 clearly shows that the drug absorption after patch application depends on the residual salt content in the semi-permeable matrix and is significantly improved by reducing the amount of the protonated form of rotigotine present in the matrix.

Fig. 2 shows the impact of the size distribution of the microreservoirs distributed in the semi-permeable matrix by comparing the sample obtained in Comparative Example 1 having a mean microreservoir size of approx. 15 μm and typical sizes between 10 and 20 μm (●) with the sample obtained in Comparative Example 2 having a mean microreservoir size of approx. 50 μm and typical sizes between 20 and 90 μm (▲). From this comparison it can be deduced that reducing the size of the matrix reservoirs significantly increases the flux across the human skin.

A comparison between the TDS of Example 1 (O) and Comparative Example 2 (▲) is shown in Fig. 3. This comparison clearly indicates that the flux across human skin is significantly enhanced by reducing the salt content and decreasing the size of the microreservoirs.

EXAMPLE 3In vitro Diffusion Experiment with transdermal drug delivery systems

5 The test was performed with a sandwich of consecutively a supportive separator membrane, skin and the TDS. Active substance that has diffused from the TDS through the skin and/or membrane dissolves in an acceptor liquid that continuously passes directly underneath the membrane; the
10 acceptor liquid was collected in tubes in a fraction collector; and the fractions were analysed for their content of rotigotine. The flux of active substance through skin was calculated by correcting for the influence of the separator membrane.

15 The diffusion cell described in Tanojo et al (Tanojo et al. "New design of a flow through permeation cell for in vitro permeation studies across biological membranes" Journal of Controlled Release (1997), 45, 41-47) was used in order to
20 conduct the experiment.

A flask containing the acceptor liquid and the assembled diffusion cells were placed in a temperature-controlled water-bath ($32.0 \pm 0.5^{\circ}\text{C}$). The acceptor liquid was
25 continuously pumped from the flask through PTFE tubing by a peristaltic pump, passed through the diffusion cells where the diffusion takes place and was then transported via PTFE tubing to test tubes that were placed in a fraction collector.

30 The required number of disks was punched out from the TDS by using a circular knife. Human epidermis, excised to a thickness of 200-300 μm from fresh donor skin (storage ≤ 36 hours at 4°C) with a dermatome (to be referred to as
35 skin) was spread out on laboratory film in petridishes. Using the circular knife the required number of disks was punched out. A disk of membrane was centred on each cell

surface. The skin disks were spread out on the membrane disks on the cell surfaces with the aid of forceps. A disk of the TDS is applied to each cell, and the cells were assembled. The experiment was then conducted in a manner
5 similar to the one described in Tanojo et al above.

Afterwards the tubes containing the collected fraction were weighed, and the contents of each tube were analysed using HPLC.

10

This experiment was carried out for the TDS of Example 1 as well as Comparative Examples 2 and 3.

Fig. 6 shows the in vitro skin permeation profile for the TDS
15 of Example 1 (●) compared to the TDS of Comparative Example 2 (O).

Fig. 7 shows the in vitro skin permeation profile for the TDS of Example 1 (●) compared to the acrylate TDS of Comparative
20 Example 3 (O).

It is clear from the data obtained that the flux across human skin may be significantly enhanced by controlling the size of the microreservoirs in the TDS while at the same time
25 providing a semi-permeable matrix, which is highly permeable for the free base of rotigotine while being impermeable for its protonated form.

CLAIMS

1. A transdermal delivery system (TDS) comprising a backing layer inert to the components of the matrix, a self-adhesive matrix containing rotigotine and a protective foil or sheet to be removed prior to use,
- 5 characterized in that
- 10 the self-adhesive matrix consists of a solid or semi-solid semi-permeable polymer
- (1) wherein rotigotine in its free base form has been incorporated,
 - 15 (2) which is saturated with rotigotine and contains said rotigotine as a multitude of microreservoirs within the matrix,
 - (3) which is highly permeable for the free base of rotigotine,
 - 20 (4) which is impermeable for the protonated form of rotigotine,
 - (5) wherein the maximum diameter of the microreservoirs is less than the thickness of the matrix.
- 25
2. The TDS according to claim 1, characterized in that the mean diameter of the microreservoirs is in the range of 0.5 to 20 μm .
- 30
3. The TDS according to claim 1 or 2, characterized in the self-adhesive matrix being free of particles that can absorb salts of rotigotine at the TDS/skin interface.
- 35
4. The TDS according to any one of claims 1 to 3, characterized in that the polymer matrix comprises a silicone-type pressure sensitive adhesive.

5. The TDS according to any one of claims 1 to 4, characterized in that the polymer matrix comprises two or more silicone-type pressure sensitive adhesives as the main adhesive components.

5

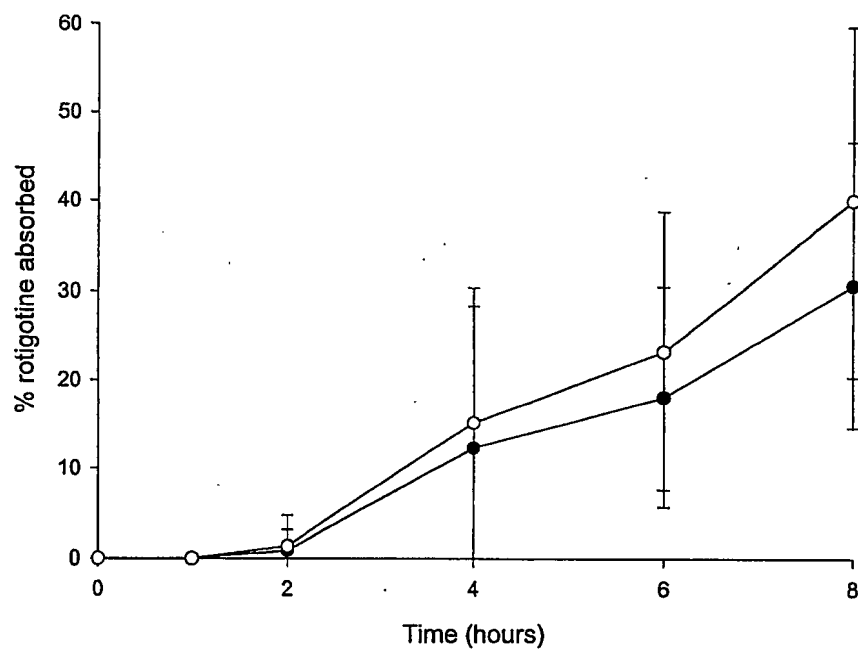
6. The TDS according to claim 5, wherein the silicone type pressure sensitive adhesive is a blend of a high tack silicone type pressure sensitive adhesive comprising polysiloxane with a resin and a medium tack silicone type pressure sensitive adhesive comprising polysiloxane with a resin.

10

7. Method for treatment of a patient suffering from a disease treatable by rotigotine by applying the TDS according to any one of claims 1 to 6 to the skin of the patient.

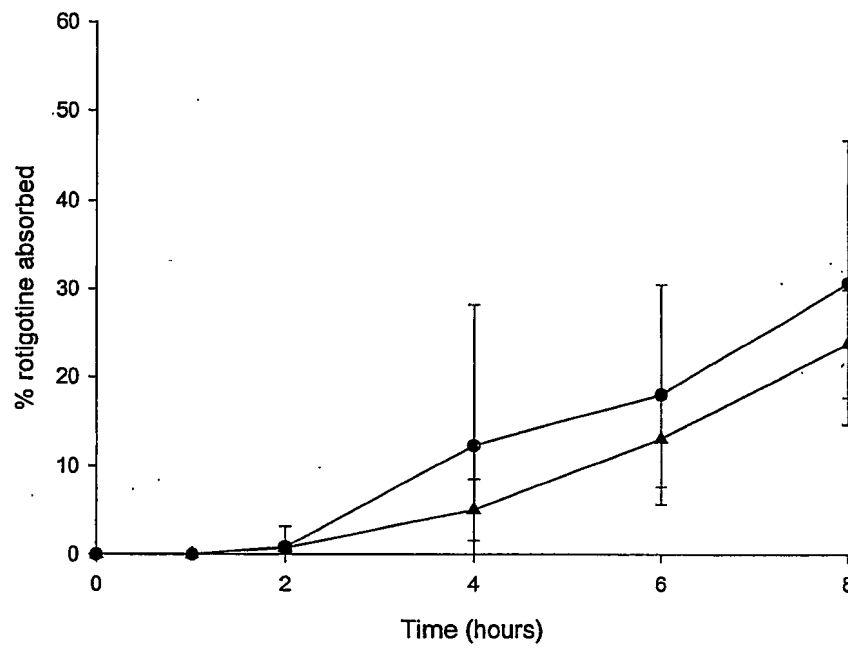
15

Fig. 1



2/7

Fig. 2



3/7

Fig. 3

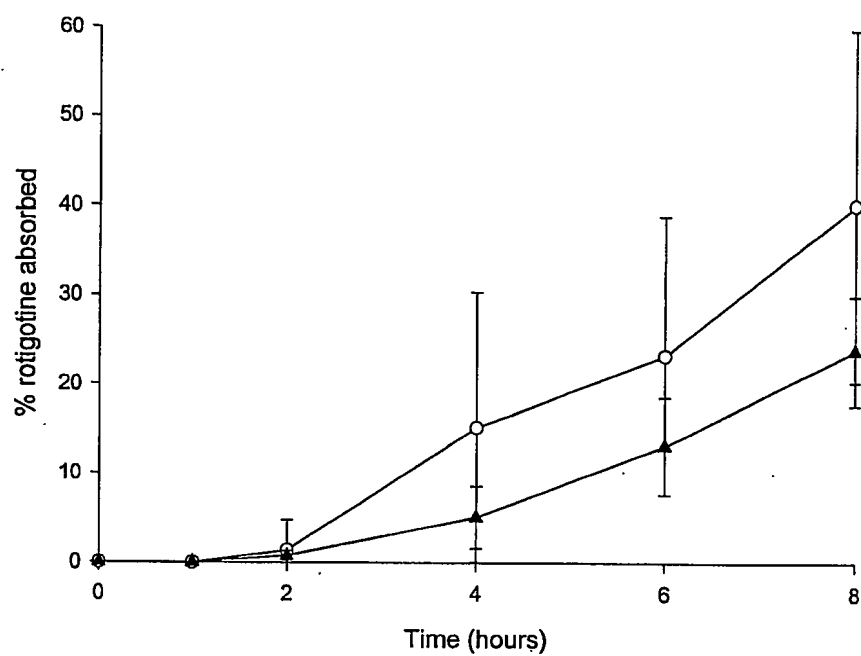


Fig. 4

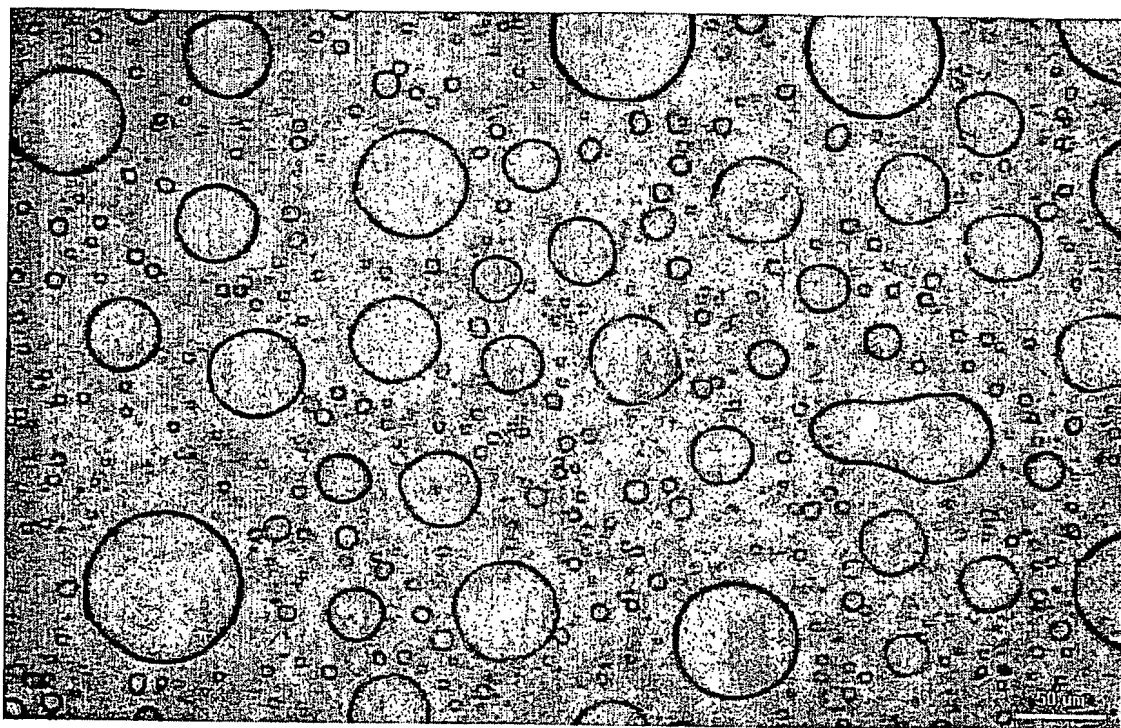
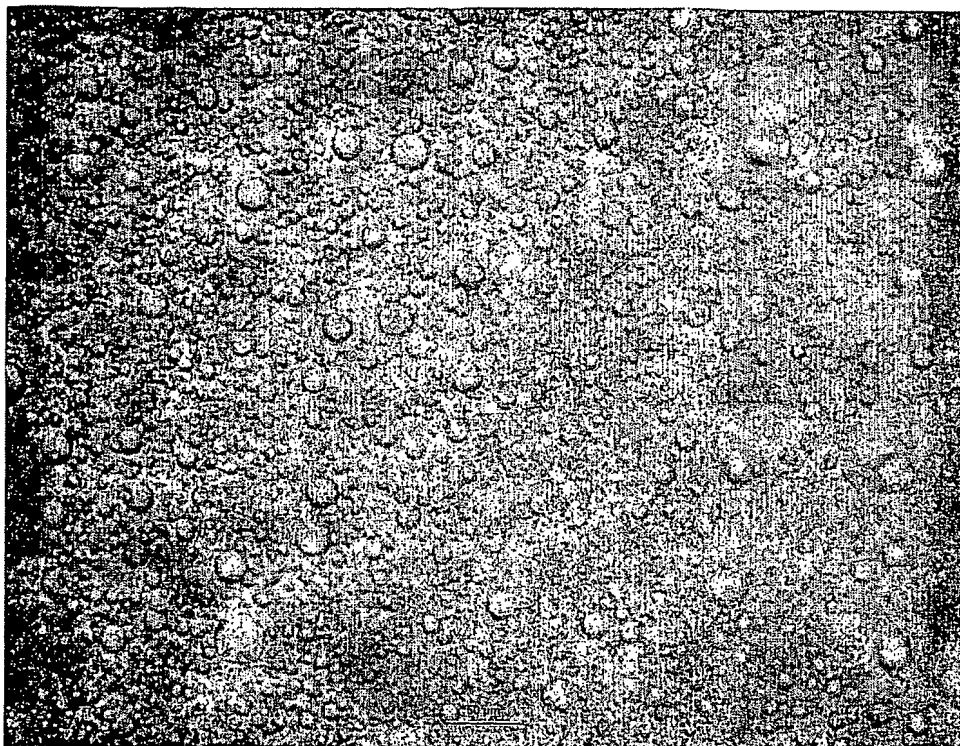


Fig. 5



6/7

Fig. 6

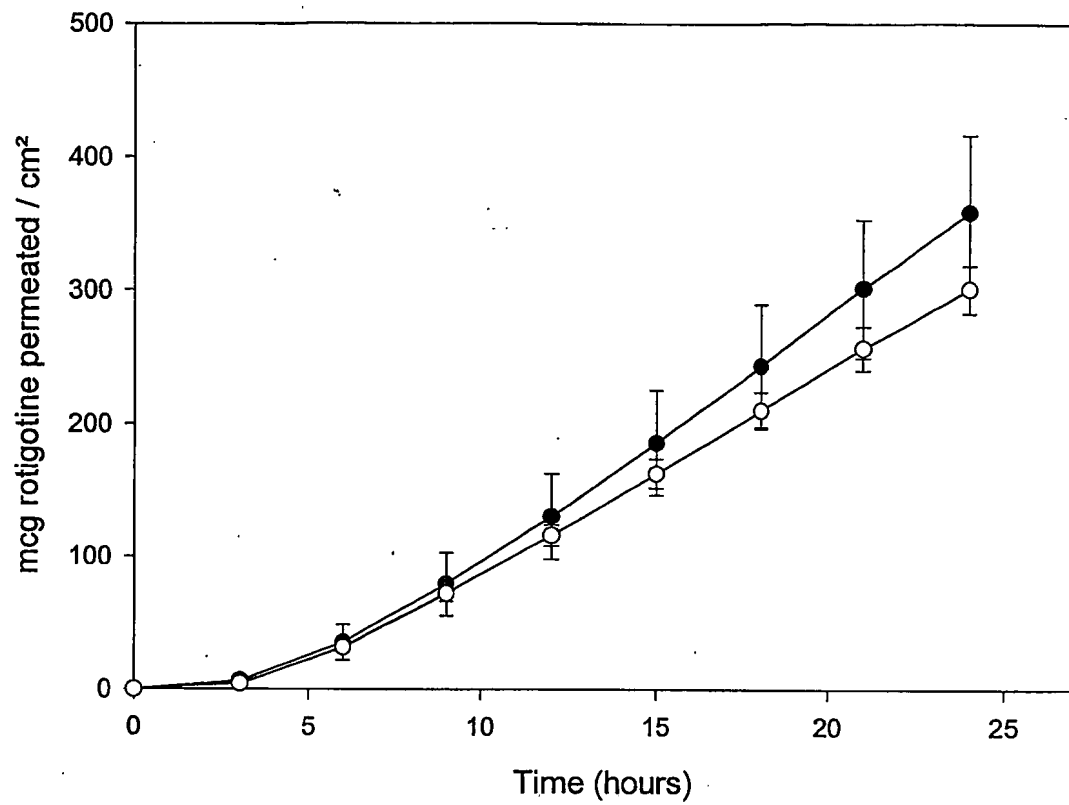
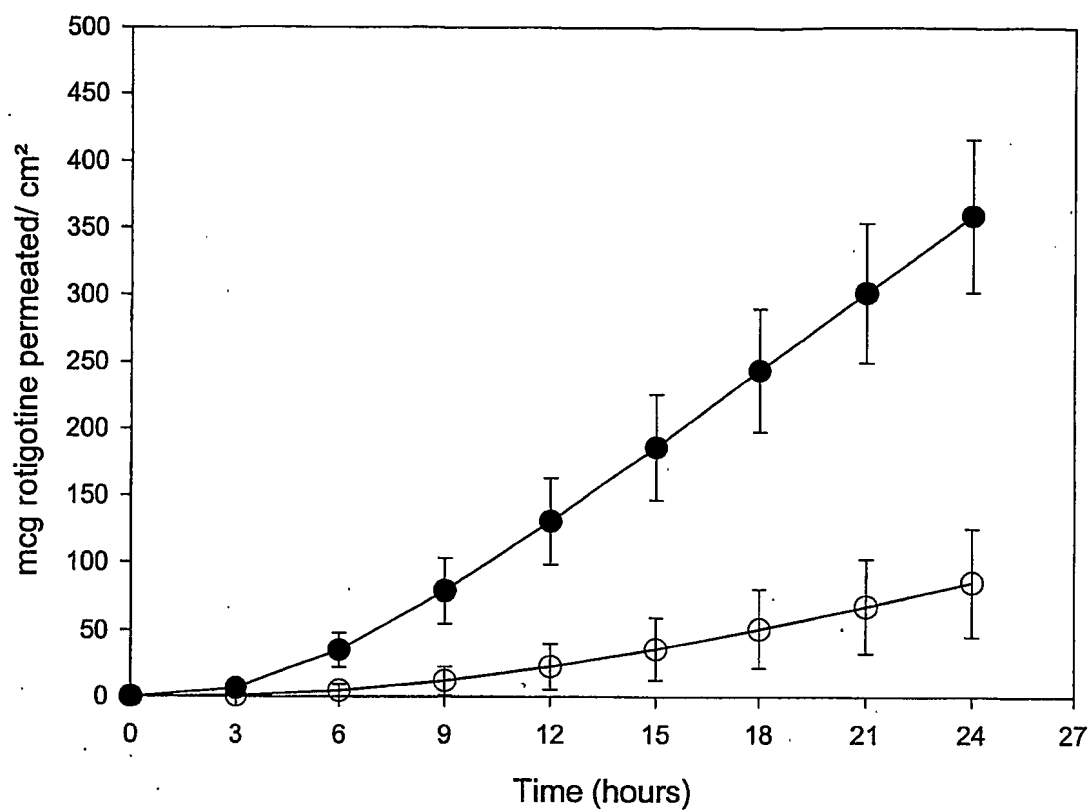


Fig. 7



INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/08320

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/38 A61K9/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 07468 A (CYGNUS THERAPEUTIC SYSTEMS) 14 April 1994 (1994-04-14) cited in the application cited in the application page 7, paragraph 4 -page 9; claims 1,12,14,15; example 15 ---	1,3-7
X	WO 99 49852 A (LOHMANN THERAPIE SYST LTS ;MUELLER WALTER (DE); PECK JAMES V (US);) 7 October 1999 (1999-10-07) page 4, paragraph 2; claims 1,6 page 8, paragraph 2 ---	1,3-7
X	DE 198 14 083 A (LOHMANN THERAPIE SYST LTS) 14 October 1999 (1999-10-14) column 2, paragraph 2; claims 1,13; examples 1,2 column 1, line 4-51 --- -/-	1,3-7

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the International filing date but later than the priority date claimed

- *T* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the International search

10 November 2003

Date of mailing of the international search report

28/11/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Kardas-Llorens, E

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/08320

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 299 900 B1 (FINNIN BARRIE CHARLES ET AL) 9 October 2001 (2001-10-09) column 6; claim 21 -----	1,7
A	DE 199 40 238 A (LOHMANN THERAPIE SYST LTS) 1 March 2001 (2001-03-01) column 1; claims 1-6; figure 1 -----	4-6
E	EP 1 256 340 A (LOHMANN THERAPIE SYST LTS ;SANOL ARZNEI SCHWARZ GMBH (DE)) 13 November 2002 (2002-11-13) page 6, paragraph 16; claims 1,2,11 paragraph '0039! -----	1,3-7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/08320

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/08320

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9407468	A	14-04-1994	US 5989586 A AT 198420 T AU 5321194 A CA 2145631 A1 CN 1089469 A DE 69329825 D1 DE 69329825 T2 DK 662822 T3 EP 0662822 A1 ES 2155073 T3 GR 3035626 T3 JP 8504757 T PT 662822 T WO 9407468 A1 US 5840336 A	23-11-1999 15-01-2001 26-04-1994 14-04-1994 20-07-1994 08-02-2001 13-06-2001 29-01-2001 19-07-1995 01-05-2001 29-06-2001 21-05-1996 30-04-2001 14-04-1994 24-11-1998
WO 9949852	A	07-10-1999	DE 19814084 A1 AT 210973 T AU 746856 B2 AU 2934199 A BR 9909313 A CA 2326630 A1 CN 1295470 T DE 59900581 D1 DK 1033978 T3 WO 9949852 A1 EP 1033978 A1 ES 2170573 T3 HK 1031196 A1 HU 0101519 A2 JP 2002509878 T NO 20004915 A NZ 507066 A PL 343255 A1 PT 1033978 T SI 1033978 T1 SK 14462000 A3 TR 200002829 T2 ZA 200005261 A	14-10-1999 15-01-2002 02-05-2002 18-10-1999 21-11-2000 07-10-1999 16-05-2001 31-01-2002 15-04-2002 07-10-1999 13-09-2000 01-08-2002 10-05-2002 28-09-2001 02-04-2002 08-11-2000 31-01-2003 30-07-2001 28-06-2002 31-10-2002 09-04-2001 22-01-2001 22-05-2001
DE 19814083	A	14-10-1999	DE 19814083 A1 AT 241343 T AU 758291 B2 AU 3597499 A CA 2326660 A1 DE 59905750 D1 WO 9949844 A2 EP 1067916 A2 JP 2002509874 T NO 20004926 A US 6620429 B1	14-10-1999 15-06-2003 20-03-2003 18-10-1999 07-10-1999 03-07-2003 07-10-1999 17-01-2001 02-04-2002 22-11-2000 16-09-2003
US 6299900	B1	09-10-2001	AU 706967 B2 AU 1713497 A WO 9729735 A1 EP 0901368 A1 JP 2000504697 T NZ 330942 A	01-07-1999 02-09-1997 21-08-1997 17-03-1999 18-04-2000 29-11-1999

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/08320

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6299900	B1	US 2002028235 A1	07-03-2002
DE 19940238	A	01-03-2001	DE 19940238 A1 01-03-2001
		AU 6995700 A	19-03-2001
		WO 0113899 A2	01-03-2001
		EP 1143939 A2	17-10-2001
		JP 2003507417 T	25-02-2003
EP 1256340	A	13-11-2002	EP 1256340 A1 13-11-2002
		AT 246919 T	15-08-2003
		DE 60100595 D1	18-09-2003
		WO 02089777 A1	14-11-2002
		EP 1325742 A1	09-07-2003
		US 2003027793 A1	06-02-2003
		ZA 200209980 A	24-02-2003